

Applicants submit that the present application is ready for examination on the merits.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

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IN THE SPECIFICATION

Please amend the specification as follows:

Please replace the paragraph at page 13, lines 3-13, as follows:

--When a phage random peptide library is prepared, it is preferred that the peptide presented by phage has a length of 3 to 15 residues. The peptide presented by phage may be directly presented by a surface layer protein of a phage particle or may be presented via a spacer having an appropriate length. Examples of the sequence of the spacer include an amino acid sequence known to successfully present a protein, such as GGGS (SEQ ID NO:[20] 32), or a peptide sequence having functions as both of an epitope and a spacer, such as an antibody epitope sequence.--

Please replace the paragraph at page 29, lines 20-27, as follows:

--The peptides are not only presented in a straight-chain form (in an unconstrained or linear form), but also can be expressed in a form having a loop structure (in a constrained or loop form) by providing two cysteine residues at both ends of the sequence to form a disulfide bond. Accordingly, the peptide represented by CX<sub>5</sub>C can be expressed by an oligonucleotide having the sequence TGT(NNK)<sub>5</sub>TGT (SEQ ID NO:29).--

Please replace the paragraph at page 29, line 28 to page 30, line 22, as follows:

--PCR amplification was performed by using 5 µg of a synthetic oligonucleotide with a biotinylated 5' end, 5'-ACTCGGCCGACGGGGC-3' (SEQ ID NO: 15), and 5 µg of non-labeled synthetic oligonucleotide, 5'-TTCGGCCCCAGCGGCCCC-3' (SEQ ID NO: 16), as

primers and 1 µg of synthetic oligonucleotide, 5'-

ACTCGGCCGACGGGGCT(NNK)<sub>n</sub>GGGGCCGCTGGGGCCGAA-3' (n = 4 to 15) (SEQ ID NO: 17-28), as a template to obtain a double strand. Taq DNA polymerase (Takara Shuzo) and an attached reaction buffer were used for PCR. A cycle composed of 95°C for 2.5 minutes, 50°C for 4 minutes and 72°C for 2.5 minutes was repeated five times in total to perform amplification and treatment at 72°C for 5 minutes was finally conducted. This PCR product was precipitated with ethanol and the obtained DNA was treated with 200 units each of *Nco*I and *Not*I (Takara Shuzo) at 37°C for 16 hours. Then, the biotinylated DNA fragment was removed by using Streptavidin Agarose (GIBCO BRL). The solution was subjected to phenol/chloroform extraction and chloroform extraction and DNA was precipitated with isopropanol. The obtained DNA was dissolved in sterilised water to obtain random insert DNA.--

Please replace the paragraph at page 43, line 23 to page 44, line 15, as follows:

--Plasmid was prepared from 950 µl of culture solution by using a FlexiPrep kit (Amersham Pharmacia Biotech). 2.5 µl (about 100 ng) of DNA corresponding to the phage identified as described above among the phagemid DNA obtained in <4> and 1.6 pmol of sequencing primer 5'-TGAATTTTCTGTATGGGG-3' (SEQ ID NO: [18]30) prepared so that it should bind to a position about 60 nucleotide upstream from the random DNA region on the phage were mixed. A cycle sequencing reaction was performed by using a prism DNA Cycle Sequencing Kit (PE Biosystems) and a PCR apparatus, PCR 9600 (Perkin-Elmer), according to the attached protocol. After the completion of the reaction, the reaction product was collected by ethanol precipitation and dissolved in formamide. Each DNA sequence was determined by using a model 377 DNA sequences (ABI) and the amino acid sequence in the

random region of the phage was analyzed. The amino acid sequences and appearance frequency are shown in Table 1.--

Please replace the paragraph at page 47, line 7 to page 48, line 16, as follows:

--A possibility that an action site of each phage peptide clone obtained as described above and that of the NS4a peptide derived from virus known to be activated by the binding to the NS3 protein were identical or overlapped was examined. A partial peptide of the NS4a peptide composed of the 18th to 40th residues from the amino terminus (referred to as 4A18-40 peptide) is known as a minimal region required to enhance the NS3 protease activity (Tanji et al., J. Virol., 69, 4017-4026, 1995). Accordingly, an influence on the binding of each phage peptide and the MBP-NS34a protein was analyzed by the phage ELISA method using a chemically synthesized 4A18-40 peptide (LTTGSVVIVGRIILSGRPAVVPD, SEQ ID NO: [19]31). 10 µg/ml of the MBP-NS34a protein to which the 4A18-40 peptide was added in an amount of 10 or 20 times in excess in a molar ratio was immobilized on each well of a 96-well microtiter plate. The plate was blocked by using 100 µl of 0.5% BSA solution prepared with 10 mM NaHCO<sub>3</sub>, and rinsed once with 200 µl of TBS buffer. 100 µl of the phage solution prepared in Example 2, <4> was added to each well of the 96-well plate on which the NS4a peptide and the MBP-NS34a protein were immobilized, and incubated overnight at 4°C. Each well was washed with 200 µl of TBS buffer four times. Then, 50 µl of horseradish peroxidase (HRP)-conjugated sheep anti-M13 phage antibodies diluted 2000 times with 5% skim milk was introduced into each well and incubated at room temperature for 1 hour.--

Page 54 (Abstract), after the last line, beginning on the next page, please delete the substitute sequence listing filed December 26, 2001, and replace it with the substitute sequence listing attached hereto.